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Clinical Neurology and Neurosurgery 103 (2001) 216–219

Clinical Neurology and Neurosurgery

www.elsevier.com/locate/clineuro

Comorbid genetic diseases, von Hippel-Lindau disease and spinocerebellar ataxia type 2, confounding the diagnosis of cerebellar dysfunction in an adolescent

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Received 21 March 2001; received in revised form 25 July 2001; accepted 1 August 2001

Abstract

The authors report a 15-year-old female who presented with difficulties in ambulation as well as difficulties with balance and penmanship. She had a known genetic risk of von Hippel-Lindau (VHL; MIM 193300) disease, with a unique VHL mutation, but had no tumors of the brain or spine to explain her symptoms. Laboratory analysis of peripheral blood lymphocytes was targeted at genetic loci associated with ataxic disorders. Allelic expansion of the ataxin-2 gene was identified. Spinocerebellar ataxia type 2 (SCA2) was diagnosed as a comorbid genetic condition in this patient. Published by Elsevier Science B.V.

Keywords: von Hippel-Lindau disease; Spinocerebellar ataxia; type 2; Cerebellum; Neurodegenerative disease

1. Introduction

Spinocerebellar ataxia, type 2, (SCA2 [MIM 183090]) is one of multiple phenotypically heterogeneous dominant spinocerebellar ataxias. It is an autosomal dominant condition that manifests as a progressive cerebellar ataxia with accompanying non-cerebellar abnormalities, which may include eye movement, sensory, and cognitive abnormalities. SCA2 results from an expansion of a CAG trinucleotide repeat on chromosome 12 in the gene for ataxin-2 [1].

2. Case report

A 15-year-old Caucasian female presented with progressive neurologic symptoms in the setting of a history of maternal von Hippel-Lindau (VHL) disease. At the time of presentation, she had a 2–3 year history of difficulty during gymnastics and while playing recreational tennis due to hand–eye coordination problems. She progressed to have difficulty with rapid ambulation, stumbling frequently. She developed slurred speech. She noted her penmanship was becoming less legible. She was unable to button shirts. She denied bowel or bladder complaints, diplopia, weakness or paresthesias. Her past medical history was notable for deafness in the left ear since infancy and a history of mild scoliosis. Her developmental history was normal with motor and verbal milestones met on time. She was reported to be a good student and was on track for high school graduation with her peers. Her adoptive parents had maintained routine screening for lesions associated with VHL disease because of her known maternal history. At 13 years old, a brain computed tomography (CT) appeared normal; at 14 years old, a brain magnetic resonance imaging (MRI) revealed a prominent vermis and atrophy of the cerebellopontine region. MRI of the spinal cord was normal. Abdominal ultrasound noted a normal pancreas and kidneys. She had no retinal angiomas.

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0303-8467/01/$ - see front matter Published by Elsevier Science B.V.
PII: S0303-8467(01)00153-6

Table 1
Results of polymerase chain reaction (PCR) and direct sequence analysis for mutations in the VHL disease gene displaying the unique mutation found in this patient

PCR product	Primer	Sequence	Mutation
Exon 1			
104/RD 101 (613 bp)	100 (F) 101 (R)	299–553+	None
Exon 2			
RD 102/103 (222 bp)	102 (F) 103 (R)	554–676+	None
Exon 3			
K59/6b (~340 bp)	K59 (F) 6b (R)	677–855 855–688	Deletion A nt 690 Deletion T nt 690

In light of her maternal history and progressively worsening neurologic status, she was referred for VHL genetic testing. She was found to be positive for a mutation in the VHL gene, having a frame shift mutation with a resultant premature stop codon representing a unique finding (see Table 1). Her adoptive parents brought her to the National Institutes of Health for further evaluation on an IRB approved protocol for comprehensive screening of VHL disease. Her neurologic examination at the National Institutes of Health was notable for truncal titubation, ataxia, scanning speech and intention tremor. In addition, she had slow saccades and saccadic pursuits as well as deafness in her left ear. No nystagmus was detected. She had diffuse hyporeflexia as well as mild hypotonia. She had impaired vibratory sense and proprioception. She had broad-based station and gait. She was unable to tandem walk. Her mild scoliosis was noted.

While at the National Institutes of Health, after obtaining informed consent and providing genetic counseling to the family, our patient underwent testing as part of the VHL disease study. Ultrasound of her abdomen revealed normal kidneys and pancreas. MRI of her brain and spine revealed mild/moderate cerebellar atrophy (see Fig. 1). There was no evidence of hemangioblastoma or retinal angioma. No abnormalities were seen in the cervical or thoracic cord. Neuroimaging of her internal auditory canals revealed no evidence of endolymphatic sac tumor (ELST). Petrous bones, inner ear, middle ear and mastoids were all normal. Audiologic examination confirmed deafness in her left ear with normal auditory acuity in her right ear. An ophthalmologic examination revealed accommodative esotropia and right amblyopia. She was also noted to have bilateral ptosis, which worsened with fatigue. None of these ocular findings are associated with VHL disease.

In light of the discrepancy between her clinical presentation and her known genetic condition, a specimen was sent for Friedreich's ataxia testing. The trinucleotide repeats in her frataxin gene were within normal limits. Hexosaminidase A and serum levels of vitamin E were both within normal limits. Nerve conduction study and electromyography were performed. The motor nerve conduction studies were normal. She had evidence of sensory neuropathy or neuronopathy affecting both upper and lower extremities.

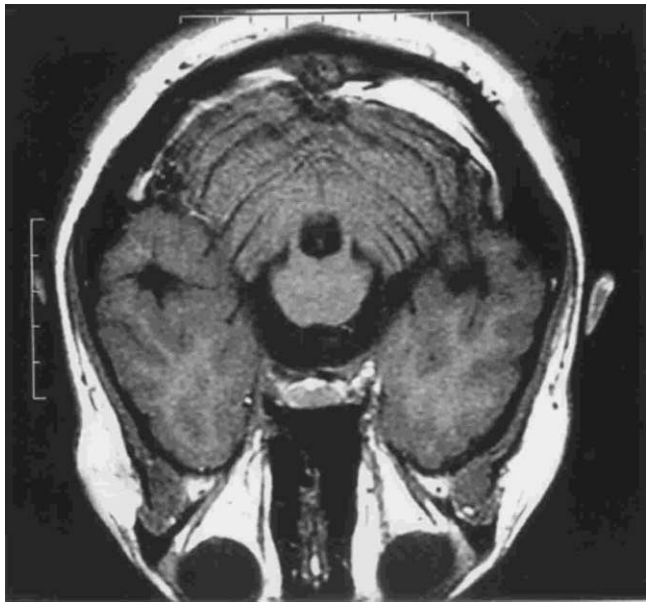

Fig. 1. Brain MRI demonstrated cerebellar atrophy characteristic of SCA2. Mild decrease in brain stem size was also noted. No VHL tumors or cysts were present.

Her peripheral blood specimen was also sent for spinocerebellar ataxia testing. The laboratory analysis included spinocerebellar ataxia, types 1–3 and 6. She was found to have a CAG trinucleotide expansion in the ataxin-2 gene on chromosome 12, consistent with the diagnosis of SCA2 (see Table 2). As she is an adopted child, we did not know whether her SCA2 was maternally or paternally derived. We know that her biological mother, as well as other maternal relatives, has VHL disease. We do not know anything of her biological father's medical history. Information on the ages of her biological parents at her birth is also unavailable, although it would be of interest since a recent analysis of Indian families indicated a possible connection between increased parental age and repeat instability [2].

Table 2
SCA2 results: The trinucleotide expansion present in allele 2 is consistent with the diagnosis.

	Patient	Reference range
Allele 1 CAG repeats	22	15–29
Allele 2 CAG repeats	46	15–29

3. Discussion

SCA2 results from a trinucleotide expansion in the gene for ataxin-2 at chromosome 12q24.1 [1]. SCA2 accounts for slightly more than 10% of patients with autosomal dominant cerebellar ataxia without retinal degeneration, referred to as ADCA I in the classification established by Harding [3,4]. The phenotype for this condition encompasses a wide spectrum. Our patient presented with slow saccades, dysarthria, decreased vibration sense, ataxia, ptosis and intention tremor, all of which is consistent with SCA2 [3,4]. The number of expanded repeats in SCA2 patients is greater than 34 units [5,6]. An inverse correlation exists between the size of the CAG repeat and the age of onset of symptoms. The patient in this case had an early onset at age 13 with 46 repeats detected. The effect of a relatively small increase in the number of additional repeats has been documented with patients carrying 37 repeats presenting in late middle age and patients with 46–50 repeats presenting during their teenaged years [6].

VHL syndrome is an autosomal dominant heritable condition with an estimated incidence of 1 in 36 000 to 1 in 40 000 live births [7]. This tumor suppressor gene was identified at 3p25–p26 [8]. Clinically these patients are at risk for multiple cerebellar and spinal cord hemangioblastomas with or without associated cysts, retinal angiomata, clear cell renal carcinoma, pancreatic neuroendocrine carcinoma, and pheochromocytoma. Brain stem involvement also occurs and often is a result of impingement from a cervicomedullary junction mass or an adjacent cerebellar mass. Rarely, supratentorial lesions occur and may cause seizures. Optic chiasm tumors can affect vision. Inner ear tumors occur in VHL and are due to ELST with the histopathologic appearance of papillary cystadenoma [7,9,10]. Abnormalities present on neurologic examination correlate with the anatomic site of the brain or spinal cord lesions, and are identifiable by neuroimaging, especially by MRI with gadolinium. Our patient exhibited neurologic symptoms known to be associated with abnormalities in the cerebellum, but she did not have any evidence of a cerebellar mass lesion on neuroimaging.

The known history of maternal VHL disease and the progressive neurologic symptoms led to further evaluation of this patient in the hope of finding a treatable cause of her condition. VHL disease is a rare condition, as is spinocerebellar ataxia. Some manifestations of these conditions can easily go unrecognized. Our patient's cerebellar signs could lead one to believe that her symptoms reflected VHL disease, which commonly involves hemangioblastomas and cysts of the cerebellum. The discrepancy between her neurological examination and her neuroimaging studies, which were remarkable for cerebellar atrophy and a slightly small pons but not for VHL disease related tumors or cysts, led to an attempt to find a second condition that might explain her symptoms. Almost all of her presenting symptoms as well as the signs seen on examination are consistent with SCA2. Ptosis is rare in SCA2 but has been previously reported [4]. Her hearing loss may be compatible with VHL disease, even in the absence of ELST, though its onset in this case is earlier than previously reported [10]. Our patient's clinical history demonstrates the importance of a neurologic examination guided by localization of the lesion with appropriate differential diagnosis generation. The family history in this patient and discovery of a unique mutation in the VHL gene acted as confounding factors in this case. The initial evaluators attributed her cerebellar symptoms to the known disease risk, expecting to find a potentially resectable cerebellar hemangioblastoma on neuroimaging. Genotyping established the existence of the comorbid condition. It is unclear to what extent, if any, the presence of the VHL disease mutation influenced SCA2 expression in this young lady. A cautionary note is sounded by this experience. If the situation had been reversed and the child had only a known family history of SCA2, there may have been a delay in the detection of a VHL related resectable cerebellar lesion, which often presents in the teenage years. The medical team charged with her care must remain mindful of the possibility of this patient developing a resectable lesion related to her VHL mutation. Although other findings have been described in association with spinocerebellar ataxia, we believe that this is the first described case of spinocerebellar ataxia in a patient with VHL syndrome.

Acknowledgements

Dr McNeil is a pediatric neurologist who is currently completing a fellowship in genetic epidemiology. The authors wish to thank the physicians and nursing staff who participated in the care of our patient during her stay at the National Institutes of Health Clinical Center.

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